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Introductory Chapter: Future Prospect of Licorice, Popular Crude Drug and Food Sweetener

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1. Classification of drugs

Drugs are classified into “over-the-counter (OTC) drugs” that are sold in drug stores and “medicinal (or ethical) drugs” that are prescribed by doctors [1] (**Figure 1**). “Herbal drug materials” and “Kampo (Japanese Traditional Medicines)” belong to OTC drugs, whereas new drugs and generics belong to the medicinal drugs. In contrast to Western medicines that recognize the drug as single compounds, Kampo medicines are a mixture of more than two components of herbal extracts. Pharmacopeia 17th edition accommodates a total of 323 herbal medicines (33 Kampo medicine + 290 herbal drug materials/formulations). Licorice is a crude drug prescribed in various herbal formulas in traditional Japanese and Chinese medicines and also used worldwide as a food natural sweetener. The origin of licorice was the root or stolon of *Glycyrrhiza uralensis* or *G. glabra* (Legminosae) [1]. Licorice contains three orders higher amounts of glycyrrhizin, as compared with other components [2].

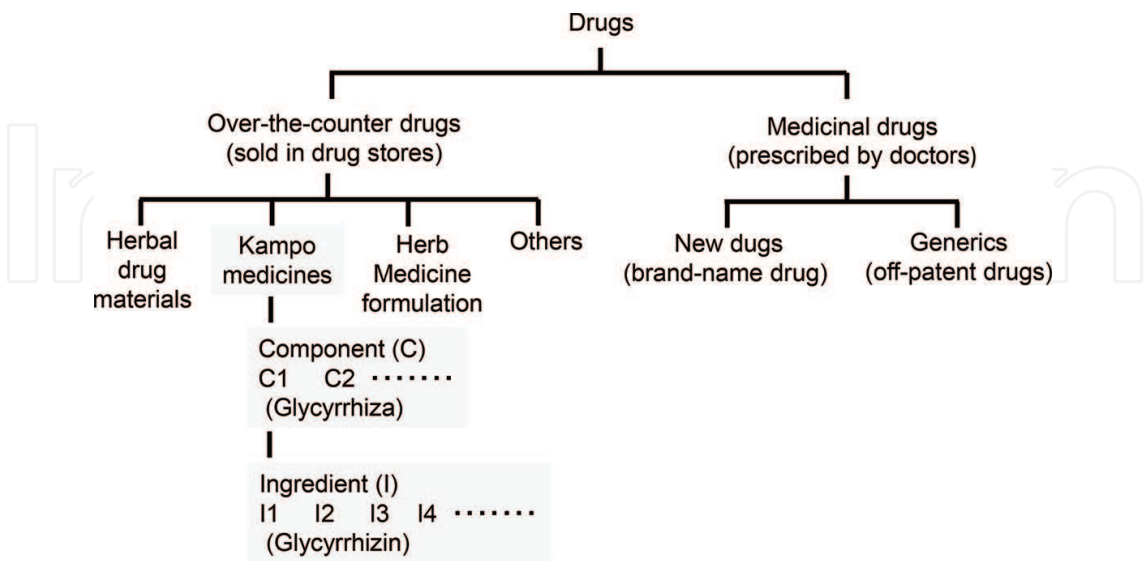


Figure 1. Classification of drugs.

2. Difference of Kampo medicine and Western medicine

To select the best Kampo medicine, the patient's condition will be first checked by the criteria of yin-yang and xu-shi categorization (activity and physical fitness) and then narrowed down by the life force, blood and colorless bodily fluids, (if necessary) followed by the five viscera theory and the pulse, tongue and belly (Figure 2). As compared with Western medicine, Kampo medicine is more empirical (rather than scientific), comprehensive (rather than analytical), global (rather than local) and personal (rather than general) and normalizes the patient's condition (rather than removing the cause of disease).

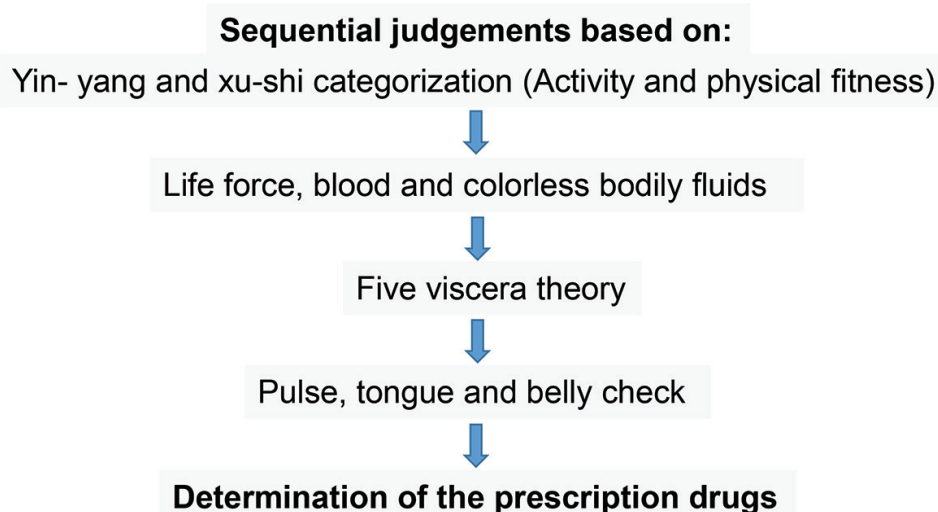


Figure 2. Process of grasping the patient's condition prior to the prescriptions of drugs.

During the business sorting work in 2009, the then Japanese regime proposed the exemption of insurance against Kampo medicines, fomentations and mouth washes, claiming that Kampo medicine is evidence less and it can be obtained very easily by anybody. However, the patients, herbalists and medical personnel moved against this proposal by means of collecting approximately one million signatures and made the proposal withdrawn. Now, in Japan, approximately 150 Kampo medicines and 200 herbal drugs used as decoctions are covered by health insurance. Among the 900 physicians who worked in the core cancer treatment hospitals, 92.4% reported having prescribed Kampo medications [3]. Nationwide, random-sampled and population-weighted telephone survey demonstrated that respondents who had used at least one complementary and alternative medicine (CAM) therapy (76.0%) were greater than those who had used orthodox Western medicine (65.6%) and that the expenditure for CAM was nearly half that of orthodox Western medicine [4]. The most common CAM practice was Kampo, which corresponded to 96.1% of CAM-practicing doctors [5]. However, it still remains to be clarified why the Kampo medicines exert beneficial effects on our body.

3. Application of Kampo medicines

Kampo medicines have been used to improve the symptoms of various diseases (Table 1). Bakumondoto, Hochuekkito and Kiyoshihaiyu, which contains licorice, have been reported to improve the symptoms of chronic obstructive pulmonary disease (COPD) [6, 7]. Daikenchuto (that contains hydroxy- α -sanshool and 6-shogaol as major ingredients) improved the intestinal motor paralysis and Crohn's disease, by increasing the RAMP (receptor activity-modifying membrane protein) 1, 2, 3, mobilizing the CGRP (calcitonin gene-related peptide) and AMD (adrenomedullin) and inhibiting the expression of pro-inflammatory cytokines (TNF- α , IFN- γ) [8]. Rikkunshito recovered the meal uptake by increasing the plasma des-acyl ghrelin level, suggesting its possible application to dyspepsia [9].

Old people experience the decline of body strength and vital function, the continuous languor, the loss of appetite and the fatigability. This kind of aging-associated characteristics cannot be remedied by Western medicines, but more easily alleviated by treating with co-agents such as Hochuekkito and Juzentaihoto. However, licorice present therein may induce hypokalemia





	Used to treat or improve the symptom of:	Presence of Licorice
Bakumondoto	Chronic obstructive pulmonary disease (COPD)	
Bofutsushosan	Insulin resistance, obesity	
Daikenchuto	Increase in intestinal blood flow, Crohn's disease	
Goreisan	Migraine	
Hachimijiogan	Arteriosclerosis, dysuria, prostatomegaly	
Hangekobokuto	Depression	
Hochuekkito	COPD, depression	
Juzentaihoto	Hepatic fibrosis, carcinogenesis	
Kakkonto	Migraine	
Keishibukuryogan	Oxidant stress, vascular endothelial damage in patient arthritis, acne	
Kiyoshihaiyu	COPD	
Maoto	Inhibition of neuraminidase	
Rikkunshito	Functional-dyspepsia, gastroesophageal reflux disease, depression	
Saikokaryukotsuboreito	Depression	
Shosaikoto	Hepatic fibrosis, carcinogenesis	
Shoseiryuto	Allergic rhinitis	
Tokishigyakukashokyoto	Sensitivity to cold, numbness	
Yokukansan	Dementia	

Table 1. Application of Kampo medicines to various diseases.

(hypertension, edema, feeling of weakness, convulsions paralysis of the extremities, arrhythmia) [10]. Shosaikoto, which also contains licorice, is known to induce interstitial pneumonia (fever, dry cough, exertional dyspnea) [11]. The use of herbal medicines is increasing all over the world and when a patient with such risk factors is prescribed an herbal medicine containing licorice, careful follow-up is required. The patient's symptoms should be carefully monitored and if no improvement in symptoms is observed, continuous treatment should be avoided.

4. Application to oral diseases

Oral cares are important to maintain the normal oral functions and prevent oral diseases. Recent report suggests an association between oral health and the risk of lacunar infarction [12]. Tooth-blushing and myofunctional therapy stimulate the secretion of saliva [13, 14]. Mouthrinsing with aqueous biocompatible 2-methacryloyloxyethyl phosphorylcholine (MPC)-polymer inhibited the increase in oral bacterial numbers, especially of *S. mutans* [15]. The inhibition of bacterial adherence and biofilm development may prevent the aspiration pneumonia and the periodontitis [16].

However, if the extent of oral diseases exceeds the capacity of oral care, we have to rely on medicines. Various Kampo medicines are used to treat oral diseases such as stomatitis, xerostomia, taste disturbance, halitosis, glossodynia, temporomandibular joint and muscle disorders (TMJ), tooth extraction and periodontal disease (**Table 2**).

	Stomatitis	Xerostomia	Taste disturbance	Halitosis	Glossodynia	TMJ	Tooth extraction	Periodontal disease	Presence of Licorice
Bakumondoto	●	●			●				Yes
Byakkokaninjinto	●	●	●		●				
Daisaikoto								●	
Goreisan	●	●			●		●		No
Hachimijiogan		●							
Hangekobokuto		●	●	●	●	●			
Hangeshoshinto	●		●	●	●				Yes
Hochuekkito	●	●			●			●	
Inchinkoto	●								
Jiinkokato		●							No
Jumihaidokuto	●								

	Stomatitis	Xerostomia	Taste disturbance	Halitosis	Glossodynia	TMJ	Tooth extraction	Periodontal disease	Presence of Licorice
Juzentaihoto	●	●	●		●				●
Kakkonto	●					●			
Kamishoyosan	●	●		●	●	●			
Kanbakutaisoto						●			
Keishikajutsubuto	●	●			●	●			
Keishibukuryogan						●			
Kikyoto							●		●
Kososan	●								
Orengedokuto	●		●	●				●	●
Orento	●			●				●	
Rikkosan	●				●		●		●
Rikkunshito	●	●	●	●	●				
Saibokuto			●		●	●			
Saikokaryukotsuboreito		●	●		●				
Saikokeishikankyoto			●						●
Saikokeishito							●		
Saireito	●	●							
Seishinrenshiin		●							
Shakuyakukanzoto						●			
Shosaikoto	●		●		●		●		
Sokeikakketsuto						●			●
Tokishakuyakusan					●	●			
Unseiin	●							●	

Table 2. Application of Kampo medicines to oral diseases.

Hangeshashashashinto showed anti-inflammatory [17], oral ulcer-induced pain-releasing [18], antimicrobial [19], antimucositis [20] and antioxidative activities [21]. Orento prevented the inflammatory responses in lipopolysaccharide-treated human gingival fibroblasts [22]. Rikkosan also induced anti-inflammatory activity [17]. Shosaikoto showed anti-inflammatory [23] and anti-hyperlipidemic and anti-atherosclerotic activities [24]. It should be noted that all these four Kampo medicines contain licorice (Table 2).

Kampo medicines are also effective to alleviate the glossodynia [25] and cancer thermotherapy-induced side effects [26–28].

5. Future direction

We sometimes experience that purification of active ingredients leads to significant loss of the biological activity. Furthermore, the amount of ingredients is different from one batch to another depending on where they are harvested. Therefore, it is essential to reconstruct the best sets of active ingredients for the standardization of the contents. First step to accomplish this is to investigate the relationship between the biological activity of structurally related compounds and chemical descriptors, using quantitative structure-activity relationship (QSAR) analysis. Once the best 3D structure is predicted, such compounds should be quickly synthesized to confirm its biological activity. This process is repeated until the satisfactory results are obtained. The next step is to determine the best combination of ingredients (**Figure 3**).

The relative potency of ingredients may depend on the type of target cells. For example, licorice flavonoids showed potent anti-HSV activity, while they were inactive against HIV infection [29]. During isolation of active ingredients, some aggregations between ingredients may happen [30]. Accumulation and analysis of such data are crucial to manufacture the best Kampo medicine.

Using QASR analysis, we recently found that anti-HSV activity of 19 flavonoids including 10 licorice flavonoids correlated well with six chemical descriptors that represent polarizability

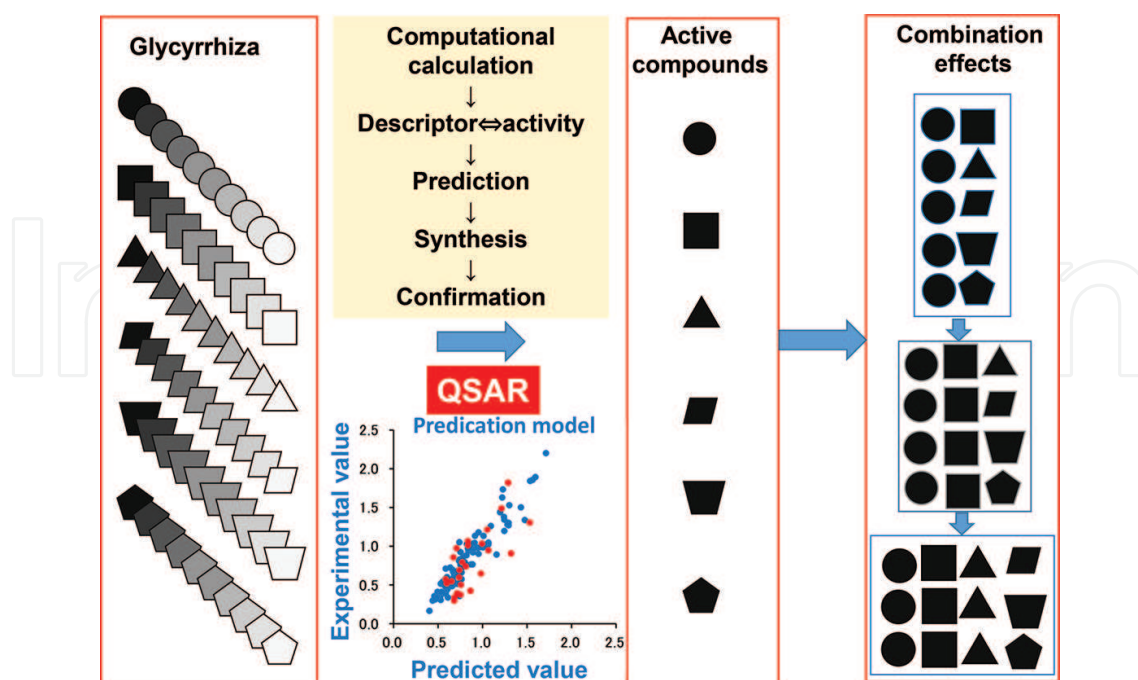


Figure 3. Chart flow to select the best combination of licorice ingredients. Each symbol is any compound. The same shapes indicated the compounds with similar structure.

(MATS5p, GATS5p), ionization potential (GATS5i), number of ring systems (NRS), atomic number ($J_Dz(Z)$) and mass ($J_Dz(m)$) ($p < 0.0001$). This result suggests that the physico-chemical properties, rather than the category of compound, are important factors in determining the anti-HSV activity [29]. The possibility that their target site may be common is under investigation.

It is expected that in the future, alternative therapy with Kampo medicines will be versioned up, in synchronization with the improvement in the personalized medicine based on the gene information.

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References

- [1] Society of Japanese Pharmacopoeia. The Japanese Pharmacopoeia Sixteenth Edition (JP XVII), Yakuji-Nippo, Tokyo (2016 March).
- [2] Kato T, Horie N, Matsuta T, Umemura N, Shimoyama T, Kaneko T, Kanamoto T, Terakubo S, Nakashima H, Kusama K, Sakagami H. Anti-UV/HIV activity of Kampo medicines and constituent plant extracts. *In Vivo*. 2012;26:1007–1013. PMID: 23160685.
- [3] Ito A, Munakata K, Imazu Y, Watanabe K. First nationwide attitude survey of Japanese physicians on the use of traditional Japanese medicine (kampo) in cancer treatment. *Evid Based Complement Alternat Med*. 2012;2012:957082. doi:10.1155/2012/957082. PMID: 23304230.
- [4] Yamashita H, Tsukayama H, Sugishita C. Popularity of complementary and alternative medicine in Japan: a telephone survey. *Complement Ther Med*. 2002;10(2):84–93. PMID: 12481956.
- [5] Watanabe S, Imanishi J, Satoh M, Ozasa K. Unique place of Kampo (Japanese traditional medicine) in complementary and alternative medicine: a survey of doctors belonging to the regional medical association in Japan. *Tohoku J Exp Med*. 2001;194(1):55–63. PMID: 11556734.
- [6] Mukaida K, Hattori N, Kondo K, Morita N, Murakami I, Haruta Y, Yokoyama A, Kohno N. A pilot study of the multiherb Kampo medicine bakumondoto for cough in patients with chronic obstructive pulmonary disease. *Phytomedicine*. 2011;18(8–9):625–629. doi:10.1016/j.phymed.2010.11.006. Epub 2010 Dec 21. PMID: 21177084.

- [7] Tatsumi K, Shinozuka N, Nakayama K, Sekiya N, Kuriyama T, Fukuchi Y. Hochuekkito improves systemic inflammation and nutritional status in elderly patients with chronic obstructive pulmonary disease. *J Am Geriatr Soc*. 2009;57(1):169–170. doi:10.1111/j.1532-5415.2009.02034.x. PMID: 19170793.
- [8] Kono T, Omiya Y, Hira Y, Kaneko A, Chiba S, Suzuki T, Noguchi M, Watanabe T. Daikenchuto (TU-100) ameliorates colon microvascular dysfunction via endogenous adrenomedullin in Crohn's disease rat model. *J Gastroenterol*. 2011;46(10):1187–1196. doi:10.1007/s00535-011-0438-2. PMID: 21808981.
- [9] Togawa K, Matsuzaki J, Kobayakawa M, Fukushima Y, Suzaki F, Kasugai K, Nishizawa T, Naito Y, Hayakawa T, Kamiya T, Andoh T, Yoshida H, Tokura Y, Nagata H, Mori M, Kato K, Hosoda H, Takebayashi T, Miura S, Uemura N, Joh T, Hibi T, Suzuki H. Association of baseline plasma des-acyl ghrelin level with the response to rikkunshito in patients with functional dyspepsia. *J Gastroenterol Hepatol*. 2016;31(2):334–341. doi:10.1111/jgh.13074. PMID: 26252950.
- [10] Ottenbacher R, Blehm J. An unusual case of licorice-induced hypertensive crisis. *S D Med*. 2015;68(8):346–347, 349. PMID: 26380428.
- [11] Nakayama M, Bando M, Hosono T, Yamasawa H, Ohno S, Sugiyama Y. Evaluation of the drug lymphocyte stimulation test (DLST) with shosaikoto [in Japanese]. *Arerugi*. 2007;56(11):1384–1389.
- [12] Taguchi A, Miki M, Muto A, Kubokawa K, Migita K, Higashi Y, Yoshinari N. Association between oral health and the risk of lacunar infarction in Japanese adults. *Gerontology*. 2013;59(6):499–506. doi:10.1159/000353707. PMID: 23942139.
- [13] Inenaga K, Inangaki T, Hosokawa R, Ono K. Parotid salivary secretion induced by stimulation of periodontal regions with toothbrush in humans. *J Med Invest*. 2009;56(Suppl):277. PMID: 20224201.
- [14] Carnaby-Mann G, Crary MA, Schmalfuss I, Amdur R. “Pharyngocise”: randomized controlled trial of preventative exercises to maintain muscle structure and swallowing function during head-and-neck chemoradiotherapy. *Int J Radiat Oncol Biol Phys*. 2012;83(1):210–219. doi:10.1016/j.ijrobp.2011.06.1954. PMID: 22014959.
- [15] Hirota K, Yumoto H, Miyamoto K, Yamamoto N, Murakami K, Hoshino Y, Matsuo T, Miyake Y. MPC-polymer reduces adherence and biofilm formation by oral bacteria. *J Dent Res*. 2011;90(7):900–5. doi:10.1177/0022034511402996. PMID: 21447697.
- [16] Martínez JA, Soto S, Fabrega A, Almela M, Mensa J, Soriano A, Marco F, Jimenez de Anta MT, Jordi V. Relationship of phylogenetic background, biofilm production and time to detection of growth in blood culture vials with clinical variables and prognosis associated with *Escherichia coli* bacteremia. *J Clin Microbiol*. 2006;44(4):1468–1474. doi:10.1128/JCM.44.4.1468-1474.2006, PMCID: PMC1448679.
- [17] Kato T, Segami N, Sakagami H. Anti-inflammatory Activity of Hangeshashinto in IL-1 β -stimulated Gingival and Periodontal Ligament Fibroblasts. *In Vivo*. 2016;30(3):257–263. PMID: 27107084.

- [18] Hitomi S, Ono K, Yamaguchi K, Terawaki K, Imai R, Kubota K, Omiya Y, Hattori T, Kase Y, Inenaga K. The traditional Japanese medicine hangeshashinto alleviates oral ulcer-induced pain in a rat model. *Arch Oral Biol*. 2016;66:30–7. doi:10.1016/j.archoral-bio.2016.02.002. PMID: 26878477.
- [19] Fukamachi H, Matsumoto C, Omiya Y, Arimoto T, Morisaki H, Kataoka H, Kadena M, Funatsu T, Fukutake M, Kase Y, Kuwata H. Effects of hangeshashinto on growth of oral microorganisms. *Evid Based Complement Alternat Med*. 2015;512947. doi:10.1155/2015/512947. PMID: 26170876.
- [20] Matsuda C, Munemoto Y, Mishima H, Nagata N, Oshiro M, Kataoka M, Sakamoto J, Aoyama T, Morita S, Kono T. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (Hangeshashinto) for infusional fluorinated-pyrimidine-based colorectal cancer chemotherapy-induced oral mucositis. *Cancer Chemother Pharmacol*. 2015;76(1):97–103. doi:10.1007/s00280-015-2767-y. PMID: 25983022.
- [21] Matsumoto C, Sekine-Suzuki E, Nyui M, Ueno M, Nakanishi I, Omiya Y, Fukutake M, Kase Y, Matsumoto K. Analysis of the antioxidative function of the radioprotective Japanese traditional (Kampo) medicine, hangeshashinto, in an aqueous phase. *J Radiat Res*. 2015;56(4):669–77. doi:10.1093/jrr/rrv023. PMID: 25883171.
- [22] Ara T, Honjo K, Fujinami Y, Hattori T, Imamura Y, Wang PL. Preventive effects of a kampo medicine, orento on inflammatory responses in lipopolysaccharide treated human gingival fibroblasts. *Biol Pharm Bull*. 2010;33(4):611–616.
- [23] Ara T, Maeda Y, Fujinami Y, Imamura Y, Hattori T, Wang PL. Preventive effects of a Kampo medicine, Shosaikoto, on inflammatory responses in LPS-treated human gingival fibroblasts. *Biol Pharm Bull*. 2008;31(6):1141–4. PMID: 18520044.
- [24] Shen YR, Inoue M, Nagatsu Y, Ogihara Y, Aburada M. Anti-hyperlipidemic and anti-atherosclerotic actions of shosaikoto (kampo medicine). *Biol Pharm Bull*. 1996;19(9):1160–1165. PMID: 8889034.
- [25] Hijikata Y, Makiura N, Kano T, Higasa K, Shimizu M, Kawata K, Mine T. Kampo medicine, based on traditional medicine theory, in treating uncured glossodynia: efficacy in five clinical cases. *Am J Chin Med*. 2008;36(5):835–847.
- [26] Ohnishi S, Takeda H. Herbal medicines for the treatment of cancer chemotherapy-induced side effects. *Front Pharmacol*. 2015 Feb;10;6:14. doi:10.3389/fphar.2015.00014. PMID: 25713534.
- [27] Aoyama T, Nishikawa K, Takiguchi N, Tanabe K, Imano M, Fukushima R, Sakamoto J, Oba MS, Morita S, Kono T, Tsuburaya A. Double-blind, placebo-controlled, randomized phase II study of TJ-14 (hangeshashinto) for gastric cancer chemotherapy-induced oral mucositis. *Cancer Chemother Pharmacol*. 2014;73(5):1047–1054. doi:10.1007/s00280-014-2440-x. PMID: 24652604.
- [28] Kono T, Takeda H, Uezono Y. Kampo medicine for the treatment of adverse effects caused by anticancer drugs [in Japanese]. *Nihon Geka Gakkai Zasshi*. 2013;114(5):251–255. PMID: 24167978.

- [29] Fukuchi K, Okudaira N, Adachi K, Odai-Ide R, Watanabe S, Ohno H, Yamamoto M, Kanamoto T, Terakubo S, Nakashima H, Uesawa Y, Kagaya H, Sakagami H. Antiviral and antitumor activity of licorice root extracts. *In Vivo*. 2016;30:777–786.
- [30] Sakagami H, Zhou Li, Kawano M, Thet MM, Takana S, Machino M, Amano S, Kuroshita R, Watanabe S, Chu Q, Wang QT, Kanamoto T, Terakubo S, Nakashima H, Sekine K, Shirataki Y, Hao ZC, Uesawa Y, Mohri K, Kitajima M, Oizumi H, Oizumi T. Multiple biological complex of alkaline extract of the leaves of *Sasa senanensis* Rehder. *In Vivo* 2010;24:735–744.